

General

Guideline Title

Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline.

Bibliographic Source(s)

Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, Morrison VA, Pini TM, Runowicz CD, Rosner GL, Shayne M, Sparreboom A, Sucheston LE, Lyman GH. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. Alexandria (VA): American Society of Clinical Oncology; 2012. 12 p. [156 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Clinical Question 1

Is there evidence that full weight–based dosing increases toxicity in obese patients with cancer?

Recommendation 1.1. The Panel recommends that actual body weight be used when selecting cytotoxic chemotherapy doses regardless of obesity status. There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight–based chemotherapy doses. Most data indicate that myelosuppression is the same or less pronounced among the obese than the non-obese when administered full weight–based doses.

Recommendation 1.2. The Panel recommends full weight–based chemotherapy dosing for morbidly obese patients with cancer, subject to appropriate consideration of other comorbid conditions. Data are extremely limited regarding optimal dose selection among the morbidly obese and other special subgroups. More studies are needed to evaluate optimal agents and agent combinations for obese and morbidly obese patients with cancer; however, on the basis of available information, it seems likely that the same principles regarding dose selection for obese patients apply to the morbidly obese.

Clinical Question 2

Is there evidence that less than full weight–based dosing compromises efficacy in obese patients with cancer?

Recommendation 2.1. The Panel recommends that full weight–based chemotherapy doses (intravenous [IV] and oral) be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure. Selecting reduced doses in this setting may result in poorer disease-free survival (DFS) and overall survival (OS) rates. There are compelling data in patients with breast cancer that reduced dose-intensity

chemotherapy is associated with increased disease recurrence and mortality. Although data in other malignancies are more limited, based on improved survival observed with chemotherapy compared with controls, a dose-response relationship exists for many responsive malignancies. Therefore, although data are not available to address this question for all cancer types, in the absence of data demonstrating sustained efficacy for reduced-dose chemotherapy, the Panel believes that the prudent approach is to provide full weight-based chemotherapy dosing to obese patients with cancer, especially those receiving treatment with curative intent. Most of the data in support of full weight-based dosing come from the treatment of early-stage disease. Data supporting the use of full weight-based doses in the advanced disease setting are limited.

Clinical Question 3

If an obese patient experiences high-grade toxicity, should chemotherapy doses or schedules be modified differently from modifications used for non-obese patients with cancer?

Recommendation 3.1. Clinicians should follow the same guidelines for dose reduction, regardless of obesity status, for all patients, depending on the type and severity of toxicity, any comorbid conditions, and whether the treatment intention is cure or palliation. There is no evidence to support the need for greater dose reductions for obese patients compared with non-obese patients. If a dose reduction is employed in response to toxicity, consideration should be given to the resumption of full weight-based doses for subsequent cycles, especially if a possible cause of toxicity (e.g., impaired renal, hepatic function) has been resolved. The Panel recognizes the need for clinicians to exercise judgment when providing care for patients who have experienced grade 3 or 4 chemotherapy toxicity. The presence of obesity alone should not alter such clinical judgment.

Clinical Question 4

Is a fixed dose (dose prescribed independently of weight or body surface area [BSA]) of cytotoxic chemotherapy ever justified? Are there unique dosing considerations for certain chemotherapeutic agents?

Recommendation 4.1. The Panel recommends consideration of fixed dosing only with select cytotoxic agents (e.g., carboplatin and bleomycin). On the basis primarily of neurotoxicity concerns, vincristine is capped at a maximum dose of 2.0 mg when used as part of the CHOP (cyclophosphamide, hydroxydoxorubicin [doxorubicin], vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) regimens. Several other cytotoxic chemotherapeutic agents have been used in clinical trials at a fixed dose independent of patient weight or BSA. However, it is not clear that fixed dosing is optimal for any of these other agents.

Clinical Question 5

How should BSA be calculated? Specifically, what is the best formula for use in the obese patient with cancer?

Recommendation 5.1. The Panel recommends that BSA be calculated using any of the standard formulas (e.g., Mosteller, DuBois and Dubois, Haycock, Gehan and George, Boyd formulas). There is no evidence to support one formula for calculating BSA over another.

Clinical Question 6

What is the role of pharmacokinetic and/or pharmacogenetic factors when determining optimal chemotherapy dose and delivery (bolus, infusional, therapeutic drug monitoring) for obese patients with cancer?

Recommendation 6.1. The Panel recommends further research into the role of pharmacokinetic and pharmacogenetic information for guiding the dosing of IV and oral chemotherapeutic agents for adult patients with cancer who are obese. It should be emphasized that there is a paucity of information on the influence of obesity on the pharmacokinetics of most anticancer drugs from properly powered trials. This is the result, in part, of empiric eligibility restrictions from the outset in clinical trials and a lack of pharmacokinetic analyses performed and published for this subpopulation. Overall, there are insufficient pharmacokinetic data to reject the recommendation to use a full weight-based dosing strategy for chemotherapeutic agents in patients with cancer who are obese, regardless of route of administration and/or infusion time.

Clinical Algorithm(s)

None available

Scope

Disease/Condition(s)

Cancer

Other Disease/Condition(s) Addressed

Obesity

Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Risk Assessment

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Pharmacology

Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for appropriate cytotoxic chemotherapy dosing for obese adult patients with cancer

Target Population

Obese adult patients with cancer

Interventions and Practices Considered

1. Full weight-based cytotoxic (intravenous [IV] and oral) chemotherapy dosing
2. Modification of chemotherapy doses and/or schedules
3. Consideration of fixed chemotherapy dosing (dose prescribed independently of weight or body surface area [BSA]) with certain cytotoxic

agents (e.g., carboplatin and bleomycin)

4. Calculation of BSA using a standard formula (e.g., Mosteller, DuBois and DuBois, Haycock, Gehan and George, Boyd)

Major Outcomes Considered

- Primary outcomes
 - Overall survival (OS)
 - Disease-specific survival
 - Disease-free survival (DFS)
 - Relapse-free survival
 - Event-free survival
 - Progression-free survival (PFS)
 - Treatment-related toxicities
- Secondary outcomes
 - Quality of life
 - Costs of care

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The MEDLINE and the Cochrane Collaboration Library electronic databases were initially searched with the date parameters of 1966 through October 2009, and articles published after the initial literature search were monitored through PubMed updates until October 2010 and added to the systematic review literature. The National Cancer Institute Physician Data Query database of clinical trials and the National Library of Medicine ClinicalTrials.gov database were also searched for ongoing trials. Electronic search results were supplemented with hand searching of selected reviews, expert consensus meeting notes, and reference lists from excluded articles. The literature search was limited to articles in English with human participants. MeSH headings and keywords searched were neoplasm, drug therapy, chemotherapy, dose, schedule, dose-intensity, obese, and overweight. The search excluded pediatric patients and patients with hematologic malignancies undergoing bone marrow transplantation. Design or publication type included studies comparing different dosing approaches, and articles had to report one or more major toxicities or response criteria. MEDLINE search terms are included in Data Supplement 3 at www.asco.org/guidelines/wbd

. A summary of the literature search results is provided in Data Supplement 4 at www.asco.org/guidelines/wbd

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Inclusion and Exclusion Review

Articles were selected for inclusion in the systematic review if they were published English language studies on cytotoxic intravenous (IV) or oral chemotherapy dosing approaches for overweight or obese patients with cancer, excluding leukemias. Data were extracted from prospective or retrospective cohort studies that addressed withholding, delaying, early cessation, or reduction of chemotherapy doses, including capping doses (e.g., at a body surface area [BSA] of 2.0 m²). Data were also extracted about treatment toxicity, disease-free survival (DFS) and overall survival (OS), and quality-of-life outcomes. Systematic reviews of randomized controlled trials (RCTs), meta-analyses, and other clinical practice guidelines were also conducted. Because of the paucity of data, this guideline does not address dosing for novel targeted agents such as tyrosine kinase inhibitors, immunotherapies (e.g., interleukin-2, interferon), or monoclonal antibodies. Pharmacokinetic studies with pharmacodynamic or clinical outcomes with appropriate controls were also included. Meeting abstracts, letters, commentaries, editorials, case reports, nonsystematic

(narrative) reviews, and studies limited to pediatric patients were excluded. Studies also were excluded if they addressed dose selection of noncytotoxic agents, such as tamoxifen or finasteride.

Number of Source Documents

- 913 potentially relevant abstracts identified by electronic searching and screened for retrieval.
- 148 articles were then retrieved for full text review.
- 56 articles were then selected that met selection criteria for data extraction.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Primary outcome measures of interest included overall survival (OS), disease-specific survival, disease-free survival (DFS), relapse-free survival, event-free survival, progression-free survival (PFS), and treatment-related toxicities. Secondary outcomes and/or other data elements of interest included quality of life and costs of care. Abstracts were reviewed, and articles were deemed appropriate for full text review and data extraction by one reviewer and reviewed by the Co-Chairs as well. Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Ontario, Canada) and data were exported into evidence tables (evidence tables provided in Data Supplements 1 and 2 at www.asco.org/guidelines/wbd [redacted]). Data were extracted by one reviewer and subsequently checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with Panel Co-Chairs, if necessary.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Panel Composition

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee convened an Expert Panel consisting of experts in clinical medicine and research relevant to appropriate chemotherapy dosing for obese adults with cancer, including medical and gynecologic oncologists, clinical pharmacologists, pharmacokinetic and pharmacogenetic experts, health services researchers, and biostatisticians. Academic and community practitioners and a patient representative were also part of the Panel.

Consensus Development Based on Evidence

The entire Panel met once in person, and additional work on the guideline was completed through teleconferences and electronic communications. The purpose of the Panel meeting was to refine the clinical questions, draft guideline recommendations, and distribute writing assignments. All members of the Panel participated in the preparation of the draft guideline document, which was then disseminated for review by the entire Panel.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was submitted to *Journal of Clinical Oncology (JCO)* for peer review. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

This guideline is based on evidence derived primarily from subgroup analyses and registry data. Refer to the "Literature Review and Analysis" sections of the original guideline document for specific evidence for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimal dosing of chemotherapy drugs or drug combinations for obese patients with cancer

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

Guideline Policy

This clinical practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary.

Limitations of the Literature

There are no prospective randomized studies comparing full weight–based chemotherapy dose selection and non–full weight–based dose selection. Retrospective analyses of randomized trials and comparative observational studies comprise the majority of the studies included in this guideline. This guideline is based on evidence derived primarily from subgroup analyses and registry data. Although the results are important, it should be clear to the reader that the evidence base for this guideline is necessarily different from those for other ASCO guidelines (e.g., Antiemetics or Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer, which rely on large, prospective randomized trials).

See the original guideline document for a more detailed discussion of the limitations of the research.

Implementation of the Guideline

Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the [ASCO Web site](#)

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, Morrison VA, Pini TM, Runowicz CD, Rosner GL, Shayne M, Sparreboom A, Sucheston LE, Lyman GH. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. Alexandria (VA): American Society of Clinical Oncology; 2012. 12 p. [156 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

Source(s) of Funding

American Society of Clinical Oncology

Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/guidelinescoi>). Members of the Panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any of these relationships.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

Availability of Companion Documents

The following are available:

- Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. Executive summary. J Clin Oncol 2012 May; 30 (13). Electronic copies: Available in Portable Document Format (PDF) from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .
- Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. Data supplements. Alexandria (VA): American Society of Clinical Oncology; 2012. 21 p. Electronic copies: Available in Portable Document Format (PDF) from the [ASCO Web site](#) .
- Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2012. 27 p. Electronic copies: Available in [Portable Document Format \(PDF\)](#) and [PowerPoint format](#) from the ASCO Web site.
- Appropriate chemotherapy dosing for obese adult patients with cancer: ASCO clinical practice guideline. Calculation tools for body surface area (BSA) and body mass index (BMI). Alexandria (VA): American Society of Clinical Oncology; 2012. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the [ASCO Web site](#) .
- Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology guideline. Clinical tools and resources. Frequently asked questions (FAQ). Alexandria (VA): American Society of Clinical Oncology; 2012. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the [ASCO Web site](#) .
- Appropriate chemotherapy dosing for obese adult patients with cancer. Podcasts by [Gary H. Lyman, MD, MPH](#) and by [Jennifer Griggs, MD, MPH](#) . Alexandria (VA): American Society of Clinical Oncology; 2012.

Patient Resources

The following is available:

- What to know: ASCO's guideline on chemotherapy doses for obese patients with cancer. 2012. Electronic copies: available in Portable Document Format (PDF) from the [Cancer.Net Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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